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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	7

DATE MAILED: 12/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/774,814	BALLEVRE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☒ Claim(s) *29-31,37 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *8* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicants' election of Group I, Claims 35-44 filed 1 October 2002 (Paper No. 6) without traverse is acknowledged.

As indicated in the attached interview summary, claim 27 is a part of linking claims which include claims 1-34 and should be examined together with the elected claims 35-44 on the merits in this Office action.

Specification/Claim Objections

The disclosure is objected to because of the following informalities:

In page 14, line 20, "6.000 rpm" should be changed to "6, 000 rpm".

In page 5, line 16 recites "aseino-glyco -macropeptide"; it is not clear whether or not the recitation refers to a term "aseino-glyco-macropeptide" or two terms "caseino-glycoprotein" and "macropeptide".

In page 9, lines 20 –22, "group A' and "group 1" is not consistent.

In page 12, line 28, "PBS" should be spelled out in full for the first instance of use.

In claim 29, "0.2mM" should be changed to "0.2 mM" with a space between 0.2 and mM. See also claims 30-31, 37 and 42.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "the mucin level"; it is not apparent as to what level and type of mucin the recitation refers as having been altered. Is the recited mucin a non-epithelial mucin? Note that mucins can be subdivided into membrane-associated class and secretory class, which differ in structure and potential function. The former includes those cell surface molecules also known as nonepithelial mucins and those proteins with mucin domains that constitute only a fraction of the protein structure. Claim 1 recites "...composition which has a protein source including amino acids..."; the recitation is unclear as to whether or not free amino acids are included in the claimed composition. Given that the recitation refers to amino acid residue building blocks of protein, the recitation would be awkward because "including amino acids" is redundantly presented. Additionally, since the "a protein source" is different from free amino acid source, the recitation needs to be clarified in this regard; the sources differ in their chemical properties, *e.g.*, in aqueous solution, lysine has a pI value of 9.74 whereas proteins containing lysine residue(s) usually have pI value around neutral. Further, claim 1 is unclear in the recitation "enterally administering" because it is vague regarding whether or not the administering the subject *via* simply eating the nutritional composition or *via* a mean of intake of the formulated composition, *e.g.*, formulated as a capsule, or *via* injection mean *etc*. See also claims 8, 14, 20, 24 and 28. The dependent claims are also rejected.

Claim 2 recites "by weight of the amino acids"; the recitation is unclear as to whether or not "the amino acids" refers to *a*) <u>total</u> amount of amino acid residues of a protein source, or *b*)

total amount of free amino acids, or a combination of *a*) and *b*). See also claims 8, 15, 20, 21, 25 and 43.

Claim 7 is indefinite as to the recitation "about 30% to about 80%"; it is ambiguous regarding what are encompassed in this limitation. The recitation appears to set "±" parameter on both ends of the % range of the disclosed composition, which would result in an ambiguous range for using claimed composition. See also claims 13, 18 and 19.

Claim 8 recites "...maintaining the synthesis of mucins in a patient..."; it not clear as to how the synthesis is maintained with regard to *de novo* biosynthesizing mucins; does "maintaining" refer to an action as opposed to null synthesis of mucins? Further, "a patient" in the recitation appears to be any subject who has any disease state(s) that may be or may not be related to mucins synthesis deficiency thereof. See also claims 14 and 24. The dependent claims are also rejected.

Claim 24 is indefinite in the recitation "the acids" because there is no antecedent basis for this recitation in the claim. The dependent claims are also included in the rejection.

Claim 28 is unclear as to the recitation "increasing the synthesis of mucins"; what is a subject is for increasing the synthesis of mucins? The dependent claims are also rejected.

Claim 32 is indefinite because the recitation "a daily recommended amount of threonine" is ambiguous without setting forth a subject to whom the amount of threonine is recommended, *e.g.*, adult, child, or infant *etc.* or different animals because different age of the subject and the animals can differ, e.g., humans as opposed to other non-primate animals, and requires distinct/different recommended amount of threonine. The dependent claims are also included in

the rejection. See also claims 33 and 34.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assessing threonine content in the mucoprotein under experimental condition, *e.g.*, starvation (example 1), in *vitro* investigate of effect of threonine concentration on the fractional synthesis rate of mucoproteins and effect of the threonine requirement on food efficiency of a diet (see examples 3 and 4), does not reasonably provide enablement for using the threonine rich nutritional composition to treat a disease state characterized by alteration of mucin in a patient, a method for maintaining mucin syntheses in a patient, and treat intestinal bacterial infection or/and inflammation in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application is directed to a nutritional increase of mucoprotein synthesis via supplement of threonine-rich composition. The specification of the instant application only sets forth guidance for threonine-rich nutritional sources administered to the culture cells or experimental animal, and for assaying for the fractional synthesis rate of mucoproteins, does not provide evidence for treating a patient suffering a disease state with the nutritional composition. Because of this reason, adequate written description requires more than a mere statement that it

is part of invention. The specification disclosure of the current application is insufficient to enable skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention/The breath of claims:

The present application is directed to treating a disease state characterized by alterations to the mucin level in a patient. The specification sets forth that the disease states can include a variety of disease states, *e.g.*, intestinal inflammatory and bacterial infection or other like disease states (see page 8, lines 28-30). However, there are no evidence (or clinic data) or guidance set forth for establishing correlation between threonine-involved mucin biosynthesis and a patient suffering from a disease state associated with *in vivo* alteration of mucin level.

The specification asserts that the nutritional composition are used as a nutritional support for patients suffering from cystic fibrosis, malignancy, chronic inflammatory bowel diseases,

ulcerative colitis and Crohn's disease, undergoing inflammatory response and other like disease states (see page 7, lines 14-21). Yet, the specification provides no support for this; absent are guidance and working examples as to clinical use of the claimed nutritional composition (note that the current claim language is directed to a treatment using threonine-rich nutritional composition).

The current disclosure sets forth a method of treating a disease state characterized by alteration of mucin, a method for maintaining mucin syntheses in a patient, and a method of treating intestinal bacterial infection or/and inflammation in a patient comprising administering to a patient a therapeutically effective amount of threonine (see page 9, lines 3-5 and claim 14). Yet, the specification is silent as to therapeutic formulation (or composition) comprising threonine-rich nutritional composition or/and other bioactive compound(s). It is unclear as to whether or not threonine is formulated with other pharmaceutical components for the administration. The disclosure is silent as to how the threonine or/and threonine-rich nutritional supplements are formulated into therapeutic composition and dosage.

The present application is also directed to increasing mucin synthesis via manipulating threonine content of nutritional composition and treating a disease state using the composition thereof. The current claims recite "threonine comprises at least 5.5%, or 7.4%, or 14%" (see claims 1, 81, 15, 24-25 and 38), which set no upper limit for use of threonine. Nowhere in the specification provides insufficient description regarding this limit. The specification asserts that threonine-rich protein source benefits mucin synthesis (see page 5, lines 12-14), *i.e.*, threonine content in the nutritional composition is proportional to mucin overproduction. Because the specification sets forth no upper limit of threonine content for the *in vivo* mucin production

which in turn is associated with disease treatment, the scope of the current claim is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation. Note that undesired high amount of threonine results in even reduced mucin synthesis (see below "unpredictability of the art").

(2) The presence or absence of working examples

No working examples are provided in the specification with respect to a direct relation between a disease state and threonine-rich nutritional composition in a patient with said disease. Yet, the results/discussion do not demonstrate how administering to the patient a threonine-rich nutrition can be effectively treating the disease state. The specification only provides guidance as to measuring threonine content in mucoprotein (example 1) and in a diet (example 2), *in vitro* analysis of incorporation of labeled threonine into mucoprotein using culture HT29-MTX cell (a human colonic carcinoma cell line) (example 3), and an effect of threonine content in the diet on the mucin synthesis rate analyzed *in vivo* in growing rats (example 4). These examples present little input on the claimed subject matter because at low (60%), normal (100%), and high (150%) threonine contents produce no statistical difference as to threonine associated fractional mucin synthetic rare (see Table 1, page 15) except extreme low threonine content (30%). Thus, these examples neither provide support for establishing a direct relation between a disease state and threonine content in the disclosed nutritional composition nor show consequence of administering to the patient in whole the threonine-rich composition.

The specification asserts that administering the nutritional composition to all of patients have improved mucus condition and resulted in the remission of Cohn's disease in most cases

(see example 2). However, no working examples or clinical date have been shown as to this regard.

(3) The unpredictability of the art:

The specification sets froth the factors: (i) the patient condition, (ii) the patient weight, (iii) the patient age, and (iv) formulation of the nutritional composition (see page 7, lines 22- 25). The current disclosure is silent as to teaching and guidance about these factors. Because these factors have great impact on the disease treatment, the outcome of the treatment is not invariable; thus it is unpredictable.

On the other aspect, the current application is additionally direct to increasing or "maintaining" mucin biosynthesis in a patient by supplementing threonine content of nutritional composition. Yet, the overproduction of mucin (mucin is defined as any of the mucoproteins that occur especially in secretions of mucous membranes) is associated with diseases, *e.g.*, Otitis media (see [0004] of Li, J. D. *et al.* Patent Application Publication No. 2002/0151491). Because the specification sets forth no upper limit of the applied threonine contents that appears to be proportional to level of mucin synthesis, and because the overproduction of mucin would lead to a disease state, the current disclosure as written "threonine comprises at least 5.5%" (see claims 1, 81, 15 and 38), "threonine comprises at least 7.4%" (see claim 24), and "threonine comprises at least 14%" (see claim 25), which are directed to unlimited threonine contents, would render the disclosure unpredictable.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. It has been shown that

baby food contains reduced threonine content (see Georgi, G. *et al.* US Pat. No. 5916621), which is contrary to the current disclosure. Since the current specification does not make clear about whether or not the threonine-rich nutritional composition can also be applied to young patient (*e.g.*, infants or child), the amount of threonine to be formulated and administered to a young patient including infants is subject to undue experimentation.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to unpredictable outcome of the disease treatment as stated in precedence and the undetermined administration parameters (*e.g.*, formulation form, dosage, the patient's health condition, body weight and age *etc.*), the scope of the claims, unpredictability of the art, the lack of sufficient guidance in the specification, it would take undue trial and error to practice the claimed invention. Because of the reasons set forth in the forgoing, the quantity of experimentation is large. The skilled artisan would be required to carry out a large body of tests for establishing a clinic correlation between threonine-rich composition and a mucin-related disease state, and research to figuring out the administration parameters suitable for the disease treatment. The mediation of maintaining the mucin synthesis in a patient does not establish reduction to practice. In view of the above, the quantity of experimentation would be exceedingly large with unpredictability for practicing the invention when it was made. The specification needs to support enabling.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to (i) clinic evidence of threonine-rich nutritional composition alone capable of treating a disease featured by an altered mucin level in a patient suffering from the

disease state, and (ii) how to maintain mucin biosynthesis in a patient *in vivo* by virtue of threonine-rich nutrition regardless of enzymatic or/and cellular regulation of the mucin synthesis. The level of skill in this art is, therefore, high and requires at least a nutritionist and biochemist at Ph.D. level as well as physician with several years of experience and knowledge in protein, lipid and carbohydrate metabolisms; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. Since the current disclosure does not set explicitly forth bioactive compound(s) formulated with the composition for the administration, and since the nutritional composition and treating a disease state using the composition per *se* do not establish reduction to practice, even an artisan who possesses knowledge and skills as mentioned in precedence will be unable to supply what is missing hereinabove.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 14, 28-34 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Bertolo, R. F. P. *et al.* (*J. Nutr.* (1998) 128, 1752-1759).

Bertolo *et al.* teach a process of administering threonine containing total parenteral nutrition (TPN) that contains all the required nutritions including protein, fat, calories, vitamins, and minerals to a patient by employing the indicator amino acid oxidation technique using labeled phenyalanine (see page 1753 and Materials and Methods section); this technique is based on the fact that the mucosa of the gastrointestinal tract has one of the most rapid turnover rates of any tissue in the body which metabolizes ~35% of phenylalanine on first pass, compared with 61% for dietary threonine, and the fact that ~ 90% of the metabolized threonine is secreted as mucosal proteins, *i.e.*, mucin proteins, and teach that (i) threonine accounted for 40% amino acid residues of intestinal mucin as important component of the gut mucosa (see page 1758, the left column, the second paragraph) and (ii) threonine is essentially required by growing gut to which mucin synthesis is proportional (see page 1758, the right column). Thus, Bertolo *et al.* teach a critical role of threonine in mucin synthesis. The Bertolo teaching is applied to claims 32-34 of the instant application.

Further, Bertolo *et al.* show threonine intake (*i.e.*, administering to a patient) index 0.6 g/kg·day by measuring the concentration of the indicator amino acid (*i.e.*, the labeled Phenylalanine) at saturation level (see Table 3 data and Figure 5). The daily recommended threonine amount is given as 0.68 g /kg·day (see page 1756, lines 1-6 form the bottom of the right column), then, the amount of recommended threonine (0.6 g/kg·day) would be 0.6/0.68 = 88% of the daily recommended threonine amount, which meets claim 32-33 limitation. Because the Table 3 data also shows that 0.8 g /kg·day level is still within the saturation, the amount of recommended threonine would be 0.8/0.68 = 1.17% of the daily recommended threonine amount, which meets the limitation of claim 34 of the current application.

Therefore, the Bertolo *et al.* reference anticipates the subject matter disclosed in the application claims 32-34.

Claims 28-31 are also rejected because of the following reasons.

Bertolo *et al.* teach at plateau (saturation) level, the amount of threonine administrated is 0.6 – 1.2 0.68 g /kg·day, for 10 ml/h administering arte (see page 1753, the right column). Calculation of the threonine molar concentration is as follows: 0.6 g /kg·day ×3 kg /119.12/10 ml/h × 24 h = 1.5 mM, wherein, (i) body weight of the subject to be administered is 3 kg, (ii) threonine molecular weight is 119.12, and (iii) one day is converted to 24 hours (h) for this calculation. Thus, the calculated concentration meets the limitation of claims 28-30.

According to Figure 2, 0.2 g /kg·day is the point into plateau; thus, 0.2 g /kg·day ×3 kg /119.12/10 ml/h × 24 h ≈ 0.5 mM, which meets the limitation of claim 31 of the instant

application. Therefore, the Bertolo *et al.* reference anticipates the subject matter set forth in the application claims 28-31.

Bertolo *et al.* teach a threonine content associated mucin synthesis (see the foregoing statement). In addition, Bertolo *et al.* teach a process of administering threonine containing total parenteral nutrition (TPN) that contains all the required nutrients including protein, fat, carbohydrates, vitamins, and minerals to a patient by employing the indicator amino acid oxidation technique (see the foregoing) and that TPN solution contains the recommended threonine contents (see Materials and Methods section, the third paragraph). Thus, the Bertolo *et al.* reference anticipates claim 14 of the current application.

Claims 1, 3-7, 40 and 42-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Demichele, S. J. (US Pat. No. 6468987).

Demichele *et al.* disclose a method for providing nutrition to a patient with ulcerative colitis (a intestinal inflammatory disease) comprising the administration of a nutritional product including a source of protein (see patent claim 32 and item d) of patent claim 14), and teach that the diet has a significant impact on mucosal eicosanoid (glyco-moiety) biosynthesis (see column 10, lines 7-9), as applied to the application claims 1 and 40. Note that mucin is a glycoprotein and incorporating eicosanoid lipid moieties into mucoprotein precursor is a part of mucin biosynthetic process.

Also, Demichele *et al.* teach the protein source comprises 75% whey protein (see column 17, line 54) and the protein is hydrolyzed (see claim 19); note that whey protein contains ~ 7.4%

of threonine by total weight of amino acid residues [see the specification at page 5, line 28-29]); so, the threonine content would be 75% × 7.4% ≈ 5.6 %, which meets the limitations set forth in claims 3-4 and 43-44 of the current application. Therefore, the Demichele *et al.* reference anticipates claims 1, 3-4, 40, 43 and 44.

Since Demichele *et al.* also teach the nutritional composition comprises lipid source and carbohydrate (see claim 14, items a) and b)) and the composition comprising 10-50% medium chain and 25-80% fish oil which is enriched in Omega-3 fatty acids that belongs to long chain triglyceride), the Demichele *et al.* reference anticipates claims 5-7 of the instant application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 20, 22, 28-30 and 32-44 are rejected under 35 U.S.C. 103(a) as being obvious over Hennebicq-Reig *et al.* (*Biochem. J.* (1998) 334, 283-295) taken with Demichele, S. J. (US Pat. No. 6468987), Trimbo, S. *et al.* (US Pat. No. 5728678) and Granados, R. R. *et al.* (US Pat No. 6187558).

Hennebicq-Reig *et al.* teach importance of threonine for mucin synthesis (see Table 4), as applied to claims 1, 20, 28 and 32 of the current application. Yet, Hennebicq-Reig *et al.* do not teach use of threonine or/and threonine rich nutritional composition for promoting growth of mucosal tissue and preventing mucosal-related disease states.

Demichele *et al.* disclose a method for providing nutrition to a patient with ulcerative colitis (a intestinal inflammatory disease) comprising the administration of a nutritional product including a source of protein (see patent claim 32, and item d) of patent claim 14), and teach that the diet has a significant impact on mucosal eicosanoid (glycoprotein) biosynthesis (see column 10, lines 7-9), as applied to the application claim 1 and 40. Note that mucin is a glycoprotein and incorporating eicosanoid lipid moieties into mucoprotein precursor is a part of mucin biosynthetic process. Also, Demichele *et al.* teach the protein source comprises 75% whey protein (see column 17, line 54) and the protein is hydrolyzed (see claim 19); note that whey protein contains ~ 7.4% of threonine by total weight of amino acid residues [see the specification at page 5, line 28-29]); so, the threonine content would be $75\% \times 7.4\% \approx 5.6\ \%$, which meets the limitation of claims 3-4 and 43-44 of the instant application. Thus, the Demichele *et al.* teaching is applied to claims 1-4, 20, 22 and 35-44 of the instant application.

Demichele *et al.* further teach the nutrition comprising lipid source and carbohydrate (see claim 14, items a) and b)) and the composition comprising 10-50% medium chain and 25-80% fish oil which is enriched in Omega-3 fatty acids that belongs to long chain triglyceride), as applied to claims 5-7 of the instant application.

Trimbo *et al.* disclose a method of providing nutritional composition to a patient suffering from a disease state; the composition contains threonine enriched protein source, *e.g.*, whey protein (see column 4, lines 8-14), as applied to claims 1-3, 20, 22, 35-36, 38-39, 40-41 and 43-44. Trimbo *et al.* teach that the nutritional composition having 23.0 g/l essential amino acids, which is equivalent to ~ 6.7 mM threonine concentration (see column 4, lines 2-3). The calculation for 6.7 mM is based on (i) threonine is an essential amino acid accounted for ~ 61% of total essential amino acids for mucin biosynthesis, (ii) the Trimbo *et al.* reference discloses threonine mole percent is 5.7 to 6.9 (see the patent claims 1 and 5), and (iii) threonine molecular weight = 119.12; thus, threonine molarity is: (61% × 23 g/l × 5.7% / 119.12)/ 1 × liter = 6.7 mM. Therefore, the Trimbo *et al.* teaching is obvious over the subject matter of claims 2, 37 and 42 of the instant application. Here, it is noted that 61% threonine versus total essential amino acids (threonine, Valine, leucine, isoleucine, methionine, lysine, pohenylalanine and tryptophan) is calculated according to data shown on Table 4 of Hennebicq-Reig *et al.*

Granados *et al.* teach the protective function of mucin in intestinal mucosal layer, and that mucin plays an active role in preventing bacterial infection of digestive tract (see column 1, lines 17-21 and 54-67); additionally, Granados *et al.* teach that mucin is rich in threonine (see column 4, lines 42-52), as applied to claims 40-41 and 43-44.

One of ordinary skill in the art would have combined the above teachings to treat intestinal bacterial infection in a patient with threonine rich nutritional composition comprising whey protein. This is because that (i) threonine is one of most important nutritional building blocks of mucin taught by Hennebicq-Reig *et al*, (ii) mucin plays an active role in preventing microorganism and other pathogen infection of intestinal epithelia, as taught by Granados *et al.* (see column 1, lines 17-22, and column 4, lines 42-43), (iii) the nutrition has a significant impact on mucosal glycoprotein synthesis, which comprises threonine-rich proteins, (*e.g.*, whey protein), lipids and carbohydrates as taught by Demichele *at al.*, and (iv) the threonine molarity taught by Trimbo *at el.* When combined, it would have offered the following advantages: (*a*) threonine can be readily formulated with proteins, *e.g.*, whey protein, (*b*) the components, *e.g.*, medium-chain triglycerides are easily absorbed and metabolized in patient, as taught by Trimbo et al. *et al.* (see column 5, lines 9-10), and (*c*) the formulated nutrition can also be applied to young patients, as taught by Demichele *et al.* (see column 2, lines 61-65).

Therefore, the skilled artesian would have been motivated to combine the teachings of the above references with the forgoing advantages to develop a method of treating a disease state including intestinal bacterial infection or/and inflammation in a patient *via* administering a therapeutic composition comprising threonine-rich nutritional supplement. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

As to claims 28-30 and 32-34, Hennebicq-Reig *et al.* teach importance of threonine for mucin synthesis (see Table 4), as applied to claim 28 and 32 of the current application. Yet,

Hennebicq-Reig *et al.* do not teach use of threonine or/and threonine rich nutritional composition for promoting growth of mucosal tissue and preventing mucosal-related disease states.

Trimbo *et al.* disclose a method of providing nutritional composition to a patient suffering a disease state wherein the composition comprises the threonine-rich protein source, *e.g.*, whey protein, and teach that the nutritional composition contains 23.0 g/l essential amino acids, which is equivalent to about 6.7 mM threonine concentration (see column 4, lines 2-3). The calculation for 6.7 mM is based on (i) threonine is an essential amino acid accounted for ~ 61% total essential amino acids for mucin biosynthesis, *i.e.*, 61% × 23 g/l, the Trimbo *et al.* reference disclose threonine mole percent is 5.7 to 6.9 (see the patent claims 1 and 5), and (ii) threonine molecular weight = 119.12; thus, the molar concentration is: (61% × 23 g/l × 5.7 % / 119.12)/ 1 × liter = 6.7 mM. Therefore, the Trimbo et al teaching is obvious over the subject matter of claims 29-30 of the instant application.

Also, the Trimbo *et al.* teaching is applied to claims 32-34 of the instant application. Trimbo *et al.* disclose threonine mole percent is 5.7 (see claim 5); given that daily recommended protein source is 1 g protein/kg/day (usually 1-2.5 g protein/kg/day), for 40 kg child, according to the Trimbo *et al.* teaching, the daily threonine requirement is about 5.7 % × 40 kg × 1 g protein/kg/day = 2.28 g; whereas the daily recommended amount of threonine is 28 mg /kg × 40 kg = 1.12 g (note that threonine requirement for child is about 28 mg, see the attachment 1); so, % of the recommended threonine amount would be 2.28/1.12 ≈ 203%; thus, the Trimbo *et al.* teaching is obvious over the application claims 32-34.

In view of the foregoing, it would have been obvious to one of ordinary skill in the art to arrive at claimed invention as whole because (i) Hennebicq-Reig *et al.* teach the important role

of threonine in mucin protein biosynthesis, and (ii) Trimbo *et al.* teach mole percent of threonine with respect to disclosed nutritional composition for a disease state. The mole percent of threonine can be converted to the molar concentration of threonine as well as daily-recommended threonine amount, the reference teaches the limitations of claims 29-30 and 32-34 of current application. The threonine content disclosed in the present application is thus not an improvement over the prior art. Therefore, the claimed invention, *i.e.*, a method of increasing mucin synthesis based on threonine-rich nutrition was *perima facie* obvious to make and use at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

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